

about the nature of these changes and the ways in which they develop. Among these changes emphysema may or may not be prominent. Indeed, as I have just mentioned, some patients who after many years of chronic bronchitis develop severe respiratory insufficiency with alveolar hypoventilation may be found to have very little emphysema. At present I think the best diagnostic term we can use for this group of patients is "chronic bronchitis with ventilatory failure." On the other hand, some patients with chronic bronchitis develop radiological and physiological changes which justify the clinician in concluding that emphysema is likely to have developed; and this conclusion can be summarized in the diagnosis "chronic bronchitis and emphysema."

The term "primary emphysema" may be applicable to the condition of a few patients. By this I mean that all the evidence available suggests that the anatomical change in the lungs, emphysema, was the first thing to appear. Such patients may later develop chronic hypersecretion in their bronchi, and they may then be said to be suffering from emphysema and chronic bronchitis. Similarly, the term "asthma" is simply a statement of a functional disorder which can be detected by physiological methods. If we wish to refer to asthma having a specific basis in allergic hypersensitivity we can use the term "allergic asthma." If a patient, after many years of chronic bronchitis or as an

accompaniment to symptoms which we believe to be due to emphysema, develops paroxysmal dyspnoea due to variable airway obstruction, we can properly say that he also has asthma; and the use of the term "asthma" in this connexion should not imply anything about aetiology.

Conclusion

In this talk I have tried to indicate the importance of clear definition of the basic terms used in medicine, the names of diseases. Many disagreements in discussions in medicine arise from failure to perceive that statements expressed in sentences in which the names of diseases occur must be translated into simple factual terms before they can be discussed intelligibly. This logical component in medical discussions is generally neglected. For this reason I have examined the manner in which the concepts both of a disease in general and of individual diseases are reached, and have tried to formulate a procedure by which this may be placed on a logical basis. And, finally, I have briefly considered the application of this procedure to some common problems in respiratory disease.

This lecture develops and extends the ideas I advanced in opening the Ciba Foundation Guest Symposium on the Definition and Classification of Emphysema in September, 1958 (*Lancet*, 1959, 1, 323).

AETIOLOGICAL FACTORS IN ABRUPTIO PLACENTAE*

BY

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PART I.—EPIDEMIOLOGY

Edward Rigby, physician, magistrate, and cultivator of mangel-wurzels, was, in 1776, the first person to distinguish between the "unavoidable" haemorrhage associated with placenta praevia and other "accidental" causes of ante-partum haemorrhage. Since that time it has been common practice to group together all accidental haemorrhages irrespective of their origin. This broad classification, while of some value in relation to clinical management, is unsatisfactory for scientific study, since the sites and causes of ante-partum haemorrhage differ widely. This communication is concerned only with haemorrhage due to abruptio placentae, or premature separation of the whole or part of a placenta implanted on the body of the uterus. Such cases constitute rather more than one-third of all cases of ante-partum haemorrhage and approximately one-half of cases of accidental haemorrhage.

The investigation reported here was undertaken to elucidate the significance of some of the clinical features of abruptio placentae and subsequently to correlate the findings with certain experimental evidence, with particular relation to folic-acid deficiency.

Material

This first series covers 23,043 consecutive deliveries occurring during the period 1952-8 in Mill Road Maternity Hospital, which serves a predominantly lower-class urban community. The figures derived from this material were used to assess the incidence of ante-partum haemorrhage from various causes and to study the clinical features of abruptio placentae. By comparing these results with those

for the total hospital population during the same period it is possible to obtain an assessment of the relative significance of individual factors.

Incidence of Abruptio Placentae

Of the 23,043 patients, 644 suffered from ante-partum haemorrhage—an incidence of 2.79% (Fig. 1). Abruptio

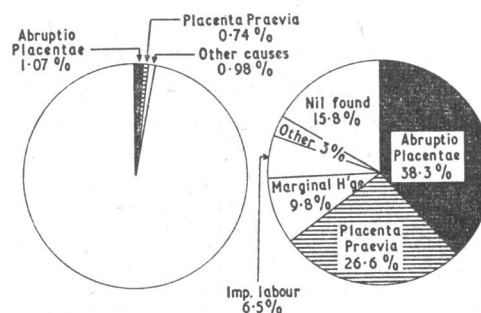


FIG. 1.—Incidence and causes of ante-partum haemorrhage in 23,043 deliveries.

placentae occurred in 247 cases (1.07%) and accounted for 38.3% of all cases of ante-partum haemorrhage. Abruptio placentae was defined as haemorrhage due to premature separation of a normally situated placenta. Cases of marginal haemorrhage without obvious separation of cotyledons were not included. In 64 cases the clinical picture and severity of the symptoms made the diagnosis of abruptio placentae obvious at the time of admission to hospital. In a further 183 cases the diagnosis was established by subsequent inspection of the placenta and

*The Katherine Bishop Harman Prize Essay, 1963.

demonstration of infarction and depression of the maternal surface of cotyledons by retroplacental clot.

Placenta praevia was demonstrated in 171 (0.74%) cases. In the remaining 226 patients with ante-partum haemorrhage bleeding was ascribed to marginal haemorrhage in 63 cases, impending labour in 42, cervicitis and vaginitis in 11, and local trauma in 8. There remained 102 cases in which the cause of the haemorrhage was obscure, and it is possible that in some of these minor degrees of abruptio placentae or placenta praevia were the causative factor.

Age and Gravidity

The incidence of abruptio placentae in relation to maternal age is shown in Fig. 2. There is an increased

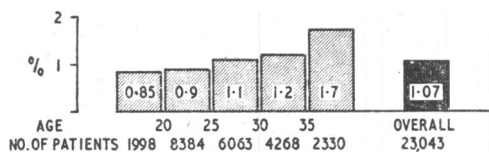


Fig. 2.—Incidence of abruptio placentae by maternal age.

incidence with maternal age, and patients over the age of 35 are twice as prone to abruption as patients under 25.

However, the important aetiological factor is revealed in Fig. 3, which shows the influence of increasing gravidity. Multigravida is associated with a significantly higher incidence of abruptio placentae, and the risk of this accident is three times greater in women who are bearing their fifth or later pregnancy than in primigravidae ($\chi^2=46$; $P<0.001$).

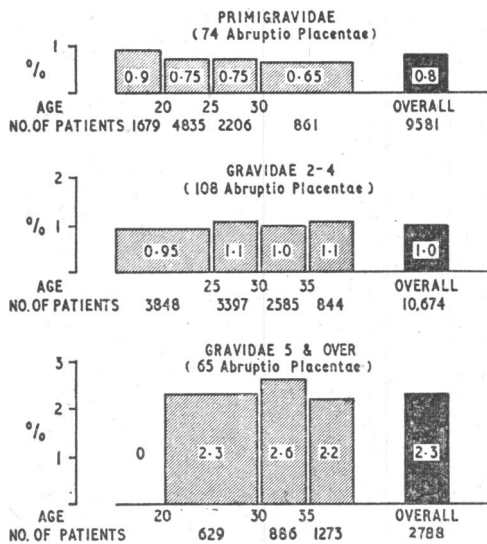


Fig. 3.—Incidence of abruptio placentae by gravidity and age.

Within each of the gravidity groups maternal age does not have any significant effect on the incidence of abruption. This suggests that maternal age of itself is not a significant factor, but that the overall trend shown in Fig. 2 is due to a concomitant gravidity trend.

Obstetric History

The inferior child-bearing capacity of the affected patients is well illustrated by examination of their obstetric careers. There were 247 patients in the series, and they had a total of 1,087 pregnancies, of which 329 (30.3%) were unsuccessful and 74 (6.8%) ended before the twenty-eighth week of gestation.

Perinatal Mortality.—Of 1,013 potentially viable infants 255 were stillborn or died in the neonatal period—a perinatal mortality rate of 25.2%, which is five times the overall hospital rate of 4.9%. Even if the index pregnancies are discounted, the perinatal mortality for previous and subsequent pregnancies was 14.4%, or three times the overall rate. The deaths were evenly divided between preceding and succeeding pregnancies. The reasons for foetal death were diverse, but the high mortality rate was mainly attributable to two factors—prematurity and recurrent abruptio placentae.

Prematurity.—Of the 1,013 infants born after the twenty-eighth week, 290 weighed 5 lb. 8 oz. (2.5 kg.) or less—an incidence of 28.6%. Discounting the index pregnancies, 141 (18.4%) out of 766 infants weighed 5 lb. 8 oz. or less, which is more than twice the overall hospital incidence of 8.8%.

Recurrence of Abruptio Placentae.—Two hundred and fourteen patients had traceable advanced pregnancies (over 28 weeks) either before or after the index pregnancy and 38 (17.8%) of these patients suffered abruptio placentae on two or more occasions. Of their 840 pregnancies, other than their index pregnancies, 47 (5.6%) were complicated by abruption, whereas if the condition is a random non-recurrent phenomenon the expected number would be 9, or less than one-fifth of the actual figure. There may be a slight bias due to the tendency to book patients with a history of ante-partum haemorrhage for hospital confinement, but it can be shown that this would not have a significant effect on the figures.

Pre-Eclampsia and Essential Hypertension

In recent years increasing doubt has arisen concerning the traditional belief that there is a marked causal relationship between pre-eclampsia and abruptio placentae. Whereas it was formerly believed that the majority of cases of abruptio placentae were due to pre-eclampsia, it is now doubtful whether this is true even in the minority (B. M. Hibbard, 1962). The false impression stems from the finding of moderate elevation of blood-pressure and albuminuria in the majority of patients with abruptio placentae. The diagnosis of pre-eclampsia or, indeed, any condition on such scant evidence is unsatisfactory, and in many cases these findings could readily be accounted for as the response to oligoemia resulting from blood loss—over-compensatory peripheral vasoconstriction resulting in mild hypertension and renal ischaemia, causing albuminuria.

Evidence against the “toxaemic” origin of abruptio placentae is found in the present series, and the main features are illustrated in Figs. 4 and 5. The standards adopted are those of Gemmell *et al.* (1954). In no case was a single blood-pressure reading accepted, and details of antenatal records were obtained from general practitioners and local health authority midwives and clinics where necessary. To confirm the diagnosis of essential hypertension an additional recording of raised blood-pressure at least one week post-partum was required.

In this series the incidence of pre-eclampsia in cases of abruptio placentae was 7.7%, only slightly higher than the figure of 5.1% for all hospital patients. Similarly, in 1,175 cases of pre-eclampsia, abruptio placentae occurred only 19 times—an incidence of 1.6% compared with an overall incidence of 1.07%. Although the lack of correlation between abruptio placentae and essential hypertension was not so marked, it was still found that only 4.9% of

patients with abruptio placentae had evidence of essential hypertension.

From Fig. 5 it is seen that pre-eclampsia was commonest in primigravidae, whereas abruptio placentae was more common in multigravidae. Pre-eclampsia was

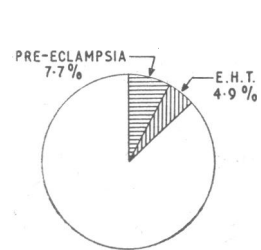


FIG. 4.—Pre-eclampsia and essential hypertension in abruptio placentae.

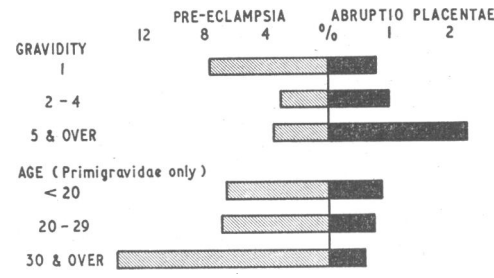


FIG. 5.—Incidence of pre-eclampsia and abruptio placentae by gravidity and age.

more common with increasing maternal age, whereas abruptio placentae showed no such trend if gravidity was discounted. This was evident when the distribution of the two conditions was studied in primigravidae only.

Pre-eclampsia tends to occur later in the third trimester than abruptio placentae. Thus, in this series, while only 26.2% of cases of pre-eclampsia were first manifested before 36 weeks' gestation, 53.9% of placental abruptions occurred in this period.

It is concluded that although pre-eclampsia and essential hypertension may be important contributory factors in a limited number of cases, they are not major features in the aetiology of abruptio placentae.

Trauma

Although trauma is often incriminated as a cause of premature placental separation it is in fact a rare occurrence and was an apparent precipitating factor in only two cases in this series. In one patient symptoms followed a fall on the abdomen, and in the other an external cephalic version had been attempted a few hours previously. Nevertheless, it is possible that many minor injuries passed unnoticed or unrecorded.

Polyhydramnios

An excessive quantity of liquor was recorded in 10 cases, which is significantly higher than expected ($\chi^2=26.5$; $P<0.001$). In three of these cases abruption immediately followed spontaneous rupture of the membranes in labour and in two abruption was preceded by high amniotomy. However, in five cases placental separation occurred before the membranes ruptured.

Unsatisfactory Foeto-Maternal Relationship

Apart from the poor obstetric performance of the patients in previous and subsequent pregnancies certain features of the affected pregnancies suggest that the mother may provide an unsuitable or inadequate environment for the foetus and placenta.

Maturity and Foetal Weight

The time of occurrence of abruptio placentae was widely distributed over the last trimester of pregnancy (Fig. 6), the greatest number being at 36-37 weeks. Although many patients were close to term before abruption occurred it is notable in this series that in over half of the cases bleeding occurred before the thirty-sixth week. Another important feature is that 40% of patients were already

established in labour at the time of admission to hospital. It is uncertain whether or not the onset of labour antedated the abruption and might therefore be an aetiological or precipitating factor, or whether labour ensued after the abruption. If the former explanation is correct, and there is a strong clinical impression that it is so in many cases, then it suggests that there is some underlying instability of the pregnancy, for the incidence of spontaneous premature labour would then be 17% compared with an overall incidence of premature labour without obvious cause of 6.5%.

The subnormal weights of the infants in relation to the period of gestation are demonstrated in Fig. 7, in which the available weights of single-born infants in the severe cases of abruptio placentae (those in which the diagnosis was immediately evident at the time of admission to hospital) are plotted against maturity. When there was a significant interval between intrauterine death and expulsion of the foetus the period of gestation at the time of death has been recorded. The heavy line represents the mean weights of random groups of single-born infants at each week of gestation from the same hospital and

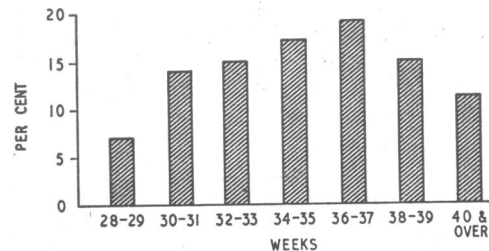


FIG. 6.—Period of gestation in relation to abruptio placentae in 247 cases.

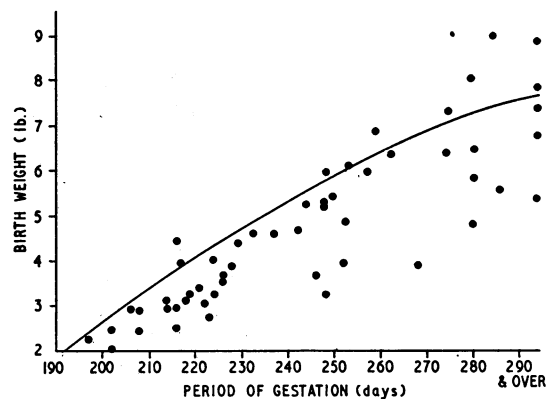


FIG. 7.—Period of gestation and birth weight in severe abruptio placentae. The line indicates the mean birth weights in relation to maturity of infants born in the hospital.

during the same period. Out of 54 infants from affected pregnancies 44 were below the expected weight for the period of gestation, and this tendency was particularly evident in infants born in the early part of the third trimester, whereas there was no significant difference between the weights of babies from affected and normal pregnancies near to term.

Congenital Malformations

Major congenital malformations were found in 11 (4.5%) out of 248 infants compared with an overall hospital incidence of 1.3%, a highly significant difference ($\chi^2=15.7$;

$P < 0.001$). In three cases the infant was anencephalic and there was associated polyhydramnios.

Other Adverse Features

Severe respiratory or cardiovascular disease was seen in 31 (12.5%) patients compared with 6.2% in the general hospital population. A strong clinical impression of inferior social status, poor nutrition, and prevalence of anaemia in the affected patients could not be confirmed in this retrospective study because of incomplete records and a high proportion of emergency admissions, but these factors are outstanding in the hospital population in general. Anaemia (haemoglobin less than 70% Haldane—10.4 g./100 ml.) is detected antenatally in approximately 20% of booked patients. A recent survey during the summer months showed that approximately one-third of the patients had no more than three meat meals weekly and nearly one-half had not more than four. Green vegetables (including salad) were eaten more than four times weekly by less than half the patients.

PART II.—ANAEMIA, ABNORMAL ERYTHROPOIESIS, AND FOLIC-ACID DEFICIENCY

The demonstration of the obstetric inadequacy of patients suffering abruptio placentae and the suggestion of deficient nutrition (see Part I) prompted a prospective investigation directed towards the maternal erythropoietic system—the most readily studied and sensitive index of general nutritional status. Concurrently with the initiation of this programme reports of a possible association between abruptio placentae and anaemia appeared, and these drew attention to the apparently high incidence of megaloblastic anaemia.

Anaemia

The suspicion of pre-existing anaemia in patients suffering from abruptio placentae is difficult to confirm because the majority of the patients are admitted as emergencies and prior haematological investigation is the exception. Further investigations at the time of admission are of limited value because of the effects of haemorrhage and are of necessity often curtailed because of the need for immediate blood transfusion and resuscitation. Moderate anaemia at the time of admission may be ascribed to haemodilution following the haemorrhage. Nevertheless, most clinicians have experienced many cases in which, in spite of apparently adequate blood transfusion, the haemoglobin concentration is subsequently found to be well below the anticipated level, and this finding is usually ascribed to faulty assessment of the blood loss. However, a more satisfactory explanation could be a subnormal haemoglobin concentration prior to the onset of haemorrhage. These features are well illustrated by the following typical case history.

Mrs. X, aged 21, came from a poor family. In her first pregnancy, prior to marriage, in 1959, she was admitted to hospital as an emergency at 34 weeks' gestation, having had approximately 20 oz. (570 ml.) of revealed ante-partum haemorrhage two hours previously. Her haemoglobin level was 57% Haldane. After transfusion with four bottles of donor blood she delivered a stillborn infant spontaneously. Total blood loss was estimated at 60 oz. (1,700 ml.). A further two bottles of blood were transfused, but on the sixth day after confinement her haemoglobin level was only 52% and it was thought that the blood loss had been underestimated. She left hospital on her own responsibility on that day. In 1960 she had a normal confinement. Antenatal and post-natal haemoglobin estimations never exceeded 78%. In 1961 she was admitted at 32 weeks' gestation, having had no antenatal care. She was in a state of shock and the clinical features were typical of

Conclusions

Exclusion of the traditional pre-eclampsia, hypertension, and trauma as major causes of premature separation of the placenta indicates the need to search for other causal factors. The positive findings in the present study are an increased risk of abruptio with high parity, a tendency to recurrence of haemorrhage in succeeding pregnancies, and the suggestion of an underlying obstetric inadequacy in many patients, as manifest by the high incidence of unsuccessful pregnancies, and premature, undersized, and malformed infants.

These findings suggest that there is a pre-existing functional defect in the foeto-maternal relationship, possibly in the placenta, which results in inadequate foetal nutrition. Both this and the tendency to abruptio may have a common aetiology. Further more detailed investigation of the clinical impression of deficient maternal nutrition and anaemia could provide the linking factor.

abruptio placentae, but there had been no revealed bleeding. After transfusion with four bottles of blood and one bottle of plasma she had a spontaneous delivery of a stillborn infant. The placenta was accompanied by 16 oz. (455 ml.) of old clot and 12 oz. (340 ml.) of fresh unclotted blood. A further two bottles of blood were administered. Seventy-two hours after confinement, in spite of an accurate estimate of the blood loss and more than adequate transfusion to correct the deficiency, her haemoglobin level was only 57%. Bone-marrow biopsy revealed a transitional pattern with early megaloblasts. Treatment with iron and folic acid was begun, but the patient again discharged herself from hospital against advice.

The occurrence of several cases of this nature over a short period of time confirmed the need for more intensive haematological investigation of patients suffering from abruptio placentae.

Megaloblastic Erythropoiesis

A positive indication of an association between anaemia, abnormal erythropoiesis, and abruptio placentae was first suggested by Hourihane, Coyle, and Drury (1960), who found that 13 out of 95 cases of megaloblastic anaemia were complicated by accidental haemorrhage. This incidence of 14% was very much higher than their overall hospital incidence of accidental haemorrhage of 2.5%. They also suggested the use of the term "megaloblastic erythropoiesis" as they were able to demonstrate megaloblastic bone-marrow changes in some patients who did not show a marked degree of anaemia, a finding subsequently confirmed by E. D. Hibbard (1962). MacKenzie and Abbott (1960) noted that ante-partum haemorrhage occurred in 4 out of 71 patients with megaloblastic erythropoiesis. Hourihane *et al.* (1960) concluded that marrow biopsy was indicated in all cases of accidental haemorrhage, and, following this recommendation, Coyle and Geoghegan (1962) found that 35 out of 77 cases of accidental haemorrhage showed megaloblastic erythropoiesis.

Folic-Acid Deficiency

The increased demands for folic acid during pregnancy have been well demonstrated by Chanarin *et al.* (1959). This is not unexpected, for folic acid is a coenzyme which is essential for the synthesis of nucleic acids, and requirements are therefore related to the extent of cell division and new tissue formation. In fact, Chanarin *et al.* showed

a close correlation between the growth rate of the foetus and the incidence of abnormal folic-acid-clearance tests. It could also be postulated that folic-acid deficiency may result in retarded or defective growth of the foetus and placenta.

It is now well established that in the British Isles megaloblastic erythropoiesis of pregnancy results specifically from a deficiency of folic acid. Investigation of the folic-acid status of patients suffering from abruptio placentae might therefore be expected to reveal similar trends to those described by Hourihane *et al.* (1960) in relation to megaloblastic anaemia.

Methods and Criteria

Folic-acid status was assessed by the formiminoglutamic acid (Figlu) excretion test according to the method described by E. D. Hibbard (1962). This was shown to be a reliable and simple test for demonstrating folic-acid deficiency. The test depends on the fact that folic acid is essential for the complete metabolic breakdown of L-histidine. In the absence of folic acid this breakdown is arrested at an intermediate stage and Figlu accumulates, ultimately to be excreted in the urine. This effect is accentuated by giving a preliminary loading dose of 10 g. of L-histidine. Figlu in the urine is readily demonstrated using high-voltage electrophoresis, as is shown in Fig. 8. The Figlu spot in the test urine is clearly visible in the upper strip.

Identification of Figlu in the specimen of urine passed five hours after the loading dose of L-histidine was considered to be a positive result and indicative of folic-acid deficiency.

Marrow biopsy was usually performed within 48 hours when haemorrhage was slight, but when haemorrhage was more severe and likely to affect the erythropoietic picture the biopsy was performed as soon as possible, prior to the Figlu-excretion test and before blood transfusion was established. Marrow biopsies were rarely performed on patients with negative Figlu tests, as it has been shown (E. D. Hibbard, 1962) that negative Figlu excretion excludes the possibility of megaloblastic erythropoiesis of pregnancy (using the term to indicate a specific folic-acid-deficiency syndrome).

Each marrow film was examined by four observers, none of whom was aware of the identity or condition of the patient concerned. Megaloblasts were identified by the characteristic appearance of their nuclear chromatin and the abnormal haemoglobinization in the cytoplasm. The

presence of forms in the early and intermediate stages of maturation along with giant metamyelocytes was adjudged to be a transitional megaloblastic pattern. Both this and the more florid patterns were regarded as megaloblastic for purposes of the investigation.

Other haematological investigations, such as peripheral blood morphology, serum iron estimation, and serum vitamin-B₁₂ level, were performed where possible and appropriate, and will be reported elsewhere.

Clinical Material

During the period October, 1961, to December, 1962, 165 patients with ante-partum haemorrhage were classified clinically by the criteria stated in Part I. There were 73 cases of abruptio placentae, 22 of placenta praevia, and 70 other ante-partum haemorrhages. Figlu-excretion tests were performed on all cases, usually within 24 hours of haemorrhage occurring. In nine cases evidence of folic-acid deficiency had been demonstrated before haemorrhage occurred. Marrow biopsies were performed on all except five of the cases with positive Figlu-excretion tests. None of these five patients was anaemic and all converted to negative Figlu excretion shortly after the appropriate treatment was started.

A control series comprised 133 consecutive patients at 32-36 weeks' gestation attending the hospital antenatal clinic. Of these, 12 failed to complete the necessary tests.

Results

All except one of the 73 cases of abruptio placentae showed positive Figlu excretion (98.6%). In the exceptional case the patient had a haemoglobin level of 63%

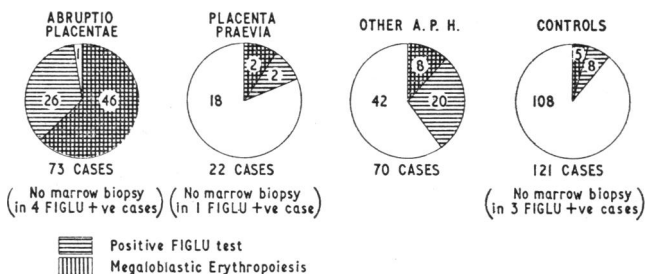


FIG. 9.—Ante-partum haemorrhage, folic-acid deficiency, and megaloblastic erythropoiesis.

in mid-pregnancy and had been treated with ferrous sulphate and folic acid without further haematological investigation. Megaloblastic erythropoiesis was detected in 46 of the 72 patients showing positive Figlu excretion. Twenty-two of the remaining patients showed normoblastic erythropoiesis, marrow biopsy being omitted in four instances (Fig. 9).

Of the 22 patients with placenta praevia 4 (18.2%) showed a positive Figlu test associated in two cases with megaloblastic erythropoiesis.

Ante-partum haemorrhage of uncertain origin occurred in 70 patients. A positive Figlu test was obtained in 28 of these cases (40%), 8 of them showing megaloblastic and 20 normoblastic erythropoiesis. In none was the bleeding severe.

The 121 controlled cases revealed 13 (10.7%) patients with a positive Figlu excretion test. Of these, five showed

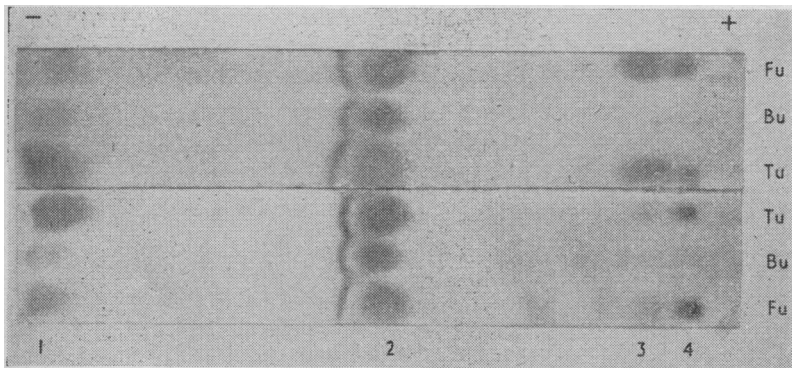


FIG. 8.—Demonstration of Figlu by high-voltage electrophoresis. Fu=Fasting urine + Figlu marker. Bu=Fasting urine without Figlu. Tu=Urine five hours after taking histidine. 1=Histidine. 2=Glycine. 3=Figlu. 4=Glutamic acid. The upper strip has been exposed to ammonia prior to developing with ninhydrin; the lower strip has been developed directly with ninhydrin.

megaloblastic and five normoblastic erythropoiesis. Three patients did not have marrow biopsy performed.

Discussion

These results indicate that there is a constant relationship between abruptio placentae and folic-acid deficiency, with a large proportion of cases also showing megaloblastic erythropoiesis. The findings suggest that folic-acid deficiency is an important factor in the aetiology of abruptio placentae, although the possibility of a common aetiology for both abruptio and folic-acid deficiency cannot be excluded at this stage.

It may be questioned whether the results of tests performed after haemorrhage has occurred are reliable indications of the state of affairs prior to haemorrhage. Positive findings might in fact be the result of haemorrhage, especially if this is severe. However, the majority of the investigations were performed before any significant cellular or biochemical changes would be likely, and the tests were consistently positive both in those cases where initial haemorrhage was slight and unlikely to be of a degree sufficient to stimulate significant erythropoiesis or to deplete existing folic-acid reserves, and in patients investigated prior to abruptio. Further, haemorrhage from causes other than abruptio placentae is not necessarily associated with folic-acid deficiency, and in such groups of patients only 10 (11%) cases showed megaloblastic erythropoiesis, compared with 63% of the patients with abruptio placentae. The relatively high incidence of folic-acid deficiency in the group of haemorrhages of uncertain origin would be compatible with the suggestion that several of these cases are in fact minor abruptio placentae.

Further evidence that Figlu excretion does not necessarily follow haemorrhage is obtained from the study of patients suffering post-partum haemorrhage, and the results will be published elsewhere.

The clinical associations and obstetric careers of the patients affected by abruptio placentae are similar to those analysed in Part I and have many features in common with recently reported series of cases of megaloblastic erythropoiesis of pregnancy. Thus most authors reporting on megaloblastic erythropoiesis find that their affected patients are above average age and that multigravidae predominate. Perinatal mortality rates were high in the series of Hourihane *et al.* (1960) (16%) and of Gatenby and Lillie (1960) (9%). Gatenby and Lillie also found a high incidence of premature labour and of prematurity by weight. This is confirmed in a series of 120 cases of folic-acid deficiency (Fig. 10) which includes most of the cases described in the present paper, and should be compared with Fig. 7 in Part I. It is seen that the majority of infants were below average weight. Eighteen (15%) out of 120 pregnancies terminated before 36 weeks' gestation, and 38 (32%) infants weighed 5 lb. 8 oz. (2.5 kg.) or less. Prematurity, whether judged by birth weight or by chronological maturity, was associated predominantly with those cases in which abruptio placentae occurred. This could be attributed to the fact that abruptio placentae was confined to patients with the more severe degrees of folic-acid deficiency, but allowance must be made for the fact that there was some selection of cases.

Two features found by other investigators to be associated with megaloblastic erythropoiesis were not prominent in the present overall series of cases of abruptio placentae. MacKenzie and Abbott (1960) found that the incidence of pre-eclampsia was increased more than threefold in their series. Hourihane *et al.* found only a slight

increase (21%) compared with an overall hospital figure of 16%. Gatenby and Lillie also found an increased incidence, but they emphasized that confusion in diagnosis was likely because of the nature of the symptoms. The other constant finding in these reports was a relatively high incidence of twin pregnancies, and MacKenzie and

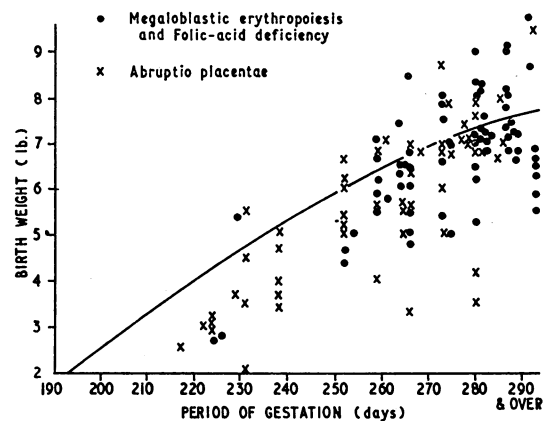


FIG. 10.—Period of gestation and birth weight in folic-acid deficiency. The line indicates the mean birth weights in relation to maturity of infants born in the hospital.

Abbott, in a special survey of twin pregnancies, showed megaloblastic erythropoiesis in 24% of cases. In our own hospital a similar association has been demonstrated. Although there are only three twin pregnancies among our 220 cases of abruptio placentae, this may be a chance finding or may be due to the fact that in recent years all patients with twin pregnancies booked for hospital confinement have been given iron and folic-acid supplements antenatally.

Prevention of Abruptio Placentae

If the association between folic-acid deficiency and abruptio placentae is a simple relation of cause and effect, then abruptio placentae would be prevented if foetal and maternal demands for folic acid could be anticipated and met. This could be achieved in two ways.

First, regular routine assessment of folic-acid status throughout pregnancy could be undertaken and appropriate treatment instituted as indicated. This is unlikely to be a practical proposition, even with the simplified tests now available, unless there are adequate laboratory facilities. Even so, it is unlikely that co-operation of patients would be as complete as would be necessary. Nevertheless, such a scheme is both practicable and desirable for those patients who run a high risk of abruptio placentae.

The second approach would be the widespread administration of folic-acid supplements throughout pregnancy. The reputed success of such schemes in reducing the incidence of megaloblastic anaemia of pregnancy suggests that prophylactic therapy of this nature might be successful for the present purpose. Indeed, vitamin supplements have been issued to pregnant women either free or at reduced prices since wartime days. Under the changed conditions of the present day a revision of these supplements would not be out of place; for there can be little doubt that folic-acid deficiency is far more likely to occur, and the consequences are far more serious than many of the other potential vitamin deficiencies against which we seek to protect our patients.

Unfortunately, there are some uncertain factors in this attractive proposition. These are related to the exact nature of the folic-acid deficiency. Basically, in these cases,

it is believed that the abnormal demands of pregnancy exceed the available supplies of folic acid, and in many cases the defect is purely a dietary inadequacy which could be prevented by improved social conditions and advice on consumption of suitable foods such as fresh fruit and green vegetables and "marmite," which are all rich in folic acid, together with supplementary therapy if necessary. However, in a significant number of cases the defect appears to be one of intestinal malabsorption. In these circumstances large doses of folic acid by mouth may be effective, but often parenteral therapy is required. In certain cases there may be faulty utilization, possibly due to the presence of folic-acid antagonists or some specific metabolic defect peculiar to pregnancy.

Conclusions

In conclusion it is evident that although abruptio placentae occurs only once in every 100 pregnancies the consequences for the mother may be serious and even fatal; in one year alone 94 bottles of donor blood and plasma were administered to patients with abruptio placentae in the hospital from which this series was drawn. Nearly two-thirds of the infants are born dead or die in the neonatal period. Indeed, the perinatal loss is comparable with that due to major deformities of the central nervous system, and is five times that due to haemolytic disease of the newborn or the hazards of breech delivery. In these circumstances comprehensive prophylactic folic-acid therapy during pregnancy requires serious consideration. It is undoubtedly indicated in those patients who have been shown to run a high risk of abruptio placentae—namely, grand multiparae, patients with anaemia, multiple pregnancies, previous unsuccessful pregnancies, and bad obstetric histories, especially when the latter include abruptio placentae. Whenever possible, such patients should have their folic-acid status assessed at frequent intervals throughout pregnancy, even though they may be receiving oral folic acid prophylactically.

By instituting a programme of this nature it is hoped that future surveys will show a significant reduction in the

incidence of this distressing and dangerous accident of pregnancy.

Summary

Abruptio placentae occurs in approximately 1% of pregnancies. A study of 320 cases occurring in approximately 27,000 deliveries reveals the following features: (a) pre-eclampsia and essential hypertension do not play a major part in the aetiology of abruptio placentae; (b) grand multiparity is a predisposing factor in abruptio placentae; (c) affected patients have unsatisfactory obstetric careers in relation to their other pregnancies—premature and undersized babies are particularly common; (d) abruptio placentae tends to recur in succeeding pregnancies; and (e) a constant relationship between abruptio placentae and folic-acid deficiency is demonstrated—megaloblastic erythropoiesis is found in a high proportion of cases.

The significance of these features is discussed in relation to other theoretical and experimental findings.

Possible preventive measures and their limitations are outlined.

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REFERENCES

- Chanarin, I., MacGibbon, B. M., O'Sullivan, W. J., and Mollin, D. L. (1959). *Lancet*, **2**, 634.
 Coyle, C., and Geoghegan, F. (1962). *Proc. roy. Soc. Med.*, **55**, 764.
 Gatenby, P. B. B., and Lillie, E. W. (1960). *Brit. med. J.*, **2**, 1111.
 Gemmell, A. A., Logan, W. P. D., and Benjamin, B. (1954). *J. Obstet. Gynaec. Brit. Emp.*, **61**, 458.
 Hibbard, B. M. (1962). *J. Obstet. Gynaec. Brit. Cwlth.*, **69**, 282.
 Hibbard, E. D. (1962). *Ibid.*, **69**, 739.
 Hourihane, B., Coyle, C. V., and Drury, M. I. (1960). *J. Irish med. Ass.*, **47**, 1.
 MacKenzie, A., and Abbott, J. (1960). *Brit. med. J.*, **2**, 1114.
 Rigby, E. (1776). *An Essay on Uterine Haemorrhage*. Johnson, London.

MULTIPLE SCLEROSIS: THERAPEUTIC TRIALS OF CHLOROQUINE, SOLUBLE ASPIRIN, AND GAMMAGLOBULIN

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In a succession of therapeutic trials previously reported from this department a standard procedure has been evolved which was designed to assess any possible effect of a particular therapeutic procedure on the natural history of multiple sclerosis. Groups of patients in the clinically active stage of the disease were allotted to treatment and control groups by a restricted randomization procedure designed to produce groups roughly comparable in all measurable respects at the beginning of treatment. Disability was scored numerically and function graded by a standard method based on that of Alexander *et al.* (1958). The patients were subjected to periodic re-examination and functional assessment by an observer who was unaware whether the patient was in the treatment or the control group. By this method intrathecal tuberculin

(Miller *et al.*, 1961c, 1962), prednisolone (Miller *et al.*, 1961a), and tolbutamide (Foster *et al.*, 1961) have been shown to exert no discernible effect on the course of the disease over a period of observation, which varied from a maximum of three years in the first trial to three months in the last.

The present paper reports the results of two separate studies carried out on similar lines. The first describes the respective effects of chloroquine, soluble aspirin, and dummy tablets on the course of multiple sclerosis over a period of 14 months, and the second the effects of repeated injections of gammaglobulin and saline respectively on two small groups of patients over a period of six months. The results of both trials were essentially negative, but they are reported together because they show certain